

DR. WILLIAM J. HEETDERKS SUMMARY STATEMENT NS43305-01 K08NST 0201
(301) 496-1447 (Privileged Communication)
wh7q@nih.gov

Application Number: 1 K08 NS43305-01
DUAL: HD

Review Group: NST
TRAINING GRANT & CAREER DEVELOP REV COMM

Meeting Dates: SRG: OCT/NOV 2001 COUNCIL: JAN/FEB 2002 ST
Requested Start Date: 04/01/2002

BOULIS, NICHOLAS M, MD
CLEVELAND CLINIC FOUNDATION
DEPT OF VIROLOGY-LERNER RES INST
9500 EUCLID AVE, NB21
CLEVELAND, OH 44195

Project Title: Targeted Motor Neuron Gene Delivery for Spasticity

SRG Action: Priority Score: 117
Human Subjects: 10-NO HUMAN SUBJECTS INVOLVED
Animal Subjects: 44-ANMLS INV.-VERIFIED, SRG CONCERNS.

PROJECT YEAR	DIRECT COSTS REQUESTED	ESTIMATED TOTAL COST
01	152,365	164,081
02	153,690	165,508
03	151,105	162,724
04	143,515	154,551
05	139,266	149,975
TOTAL	739,941	796,839

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

NOTE TO APPLICANT FOLLOWS SUMMARY STATEMENT.

RESUME AND SUMMARY OF DISCUSSION: This is an application for a K08 Mentored Clinical Scientist Development Award by Dr. Nicholas Boulis from the Cleveland Clinic Foundation, Cleveland, OH. Dr. Boulis proposes to develop and test viral vectors for use in delivery of agents for therapeutic intervention in the CNS. The main focus will be the construction of recombinant adeno-associated virus (rAAV) specifically targeted to spinal cord motor neurons. The vectors will be tested first in cell culture. A spasticity model will be used to test the efficacy of these vectors in a simple yet clinically relevant system. The Panel indicated that Dr. Boulis was a great applicant, who had already produced much scientific work. The Panel expressed much interest on the new work of Dr. Boulis about cell type specificity. The applicant, institution and proposal were all considered outstanding. The Panel, however, expressed its strong reservations about the lack of details on the use of vertebrate animals in this project (see Administrative Critiques). The Panel enthusiastically approved

this application.

DESCRIPTION (provided by applicant): Technological advancements have provided neurosurgery with new paradigms for the restoration of neural function. The dual emergence of accurate stereotaxis and deep brain stimulation (DBS) have generated a revolution in the application of targeted neuromodulation applied to movement disorders, epilepsy, eating disorders, obsessive compulsive disease, and pain (Appendix C). Nonetheless, because DBS depends on the focused delivery of electric current, it is incapable of pharmacological specificity. Rather than delivering electric current, viral vectors can alter synaptic function with molecular specificity. Further, vector tropism can be modified, creating the potential for system specific neuronal gene delivery. The experiments outlined in this proposal attempt to develop a vector capable of both neural tropism and neuromodulation. To test these concepts, we propose to develop a recombinant adeno-associated virus (rAAV) capable of synaptic inhibition and motor neuron tropism. We have chosen the spinal reflex arc as a simple mammalian functional system amenable to neuromodulation. In addition, the functional disorder, spasticity, provides a target for the study of applied neuromodulation. We hypothesize that an rAAV vector capable of specific motor neuron inhibition will have therapeutic efficacy in animal models of spasticity. In addition to providing a novel approach to spasticity, data from these studies will permit the rational design of rAAV vector(s) for application to motor neuron disease (ALS) and stereotactic neuromodulation. There are 3 Aims: 1) Construct novel vectors capable of focused synaptic inhibition, 2) develop strategies for targeted gene delivery to motor neurons with rAAV, 3) apply targeted rAAV capable of synaptic inhibition in models of spasticity. The applicant has developed a focused interest in the neural basis for behavior in both normal and pathological states. His early training in simple systems neurophysiology, and later training in biochemistry and molecular biology have prepared him for a career in the study of focused gene-based neuromodulation. His appointment to the Cleveland Clinic Foundation will give him access to one of the most active programs in Functional Neurosurgery, and create opportunities for clinical application of his work.

CRITIQUE 1:

This is an exceedingly well-written, thoughtful and organized proposal that addresses an important problem. The background section provides an excellent overview of the problem and potentials of gene therapy in the CNS. A particular attraction is the placement of gene therapy in the context of existing treatments for CNS disorders. As the applicant is a practicing neurosurgeon carrying out state-of-the-art therapies such as deep brain stimulation, such perspective is highly useful.

Successful gene therapy, particularly in the CNS, faces numerous obstacles. It is to the credit of the applicant that these are recognized and strategies to overcome them are incorporated into all aspects of the proposal. The idea of using the tetanus toxin light chain as an inhibitor of synaptic release is very clever. Although it is possible that the inhibition will be too complete, the demonstration that it works at all (gets into the cell and affects synaptic activity) is worth a great deal. The use of the experimentally convenient but clinically limited adenovirus vector in Aim 1 will allow a relatively rapid test of this idea. Studying cells in culture as a prelude to in vivo work is

also well justified. Only then will the applicant move onto the more cumbersome but potentially valuable rAAV work.

The second Aim will tackle a second major hurdle gene therapy - cell type specificity of delivery. The ideas here are also well thought out. The rational modification of the cap gene is a promising, albeit time-consuming strategy. Again, success with this (or any other method) is far from assured at this point. However, enthusiasm for the overall approach remains high because of the depth of thinking about roadblocks and alternatives. In addition, these studies will be greatly aided by drawing on the expertise of the mentor's laboratory in viral pathogenesis. Ultimately, it is the harnessing and re-engineering of these processes that will lead to the targeting solution.

The third Aim is the natural next step for these experiments. The choice of the simple spasticity model is a good one. A particular strength is the careful and thorough design and testing of the animal models. The use of multiple models and diverse assays will greatly increase the quality of the data. In turn, this data will provide for more accurate and generally useful interpretations as well as the design of new experiments to improve the system. This problem is difficult enough without swinging for the fences with the first set of vectors. Again, success is uncertain. However, it seems likely that we will gain valuable insights and information even if the therapeutic benefit is not achieved.

Candidate: Dr. Nicholas Boulis is an outstanding young scientist. He has a wide range of research experience dating back to his time as an undergraduate. Thus he can draw on a diverse and powerful repertoire of approaches. He has already used first-generation adenovirus vectors in studies on spinal cord and is thus familiar with the possibilities and pitfalls of this procedure. This background, combined with his clinical training in neurosurgery, makes for a potent combination.

Environment: The environment at the Cleveland Clinic is excellent. The mentor, Amiya Benerjee, heads a highly active laboratory that will support the proposed studies. In addition, the applicant's continued affiliation with the PFUND group at the University of Michigan will give him further access to the cutting-edge developments in gene therapy. The institution is clearly very supportive, already allowing 50% time for research, with a guarantee of continued protected time after securing external funding. In addition, he also has an institutional commitment for the support of 2 research assistants.

Conclusion: This is an outstanding proposal from a highly talented clinical investigator in the early stages of his career. The strengths are the thoughtfulness, clarity, focus and scope of the experimental design. The potential for making important strides toward gene therapy in the CNS is real.

CRITIQUE 2:

Candidate: Over the course of Dr. Boulis' undergraduate training at Yale and his medical training at Harvard, he has conducted research under the supervision of 5 individuals, the results of which have led to the publication of 11 peer-reviewed manuscripts. Studies included: 1) Analyses of hemispheric asymmetry in human emotional processing using psychophysical techniques, 2)

analyses of cellular and synaptic plasticity underlying leech behavior using behavioral and electrophysiological techniques, 3) analyses of learning, memory and anxiety in the rat using behavioral, pharmacological, biochemical and electrophysiological techniques, 4) analyses of the role that proteases play in development of neuritic tangles and plaques in Alzheimer's disease using molecular biology techniques, and 5) analyses of optic nerve regeneration in goldfish using cell culture and biochemical techniques. During his 6 year residency training period in the Department of Neurosurgery at the University of Michigan, Dr. Boulis has worked closely with 2 individuals, the results of which have led to the publication and submission of 6 scientific research papers. In addition he published 2 clinical studies, 2 chapters and several case reports during this period of time.

The research that he conducted during his residency training was focused on the application of viral gene therapy to treatment of spinal cord trauma and motor neuron disease. Dr. Eva Feldman and Dr. Michael Imperiale served as his primary supervisors during this time and will continue to collaborate with Dr. Boulis, as he establishes his research program at the Cleveland Clinic. While working under the supervision of Dr. Feldman, Dr. Boulis developed techniques to deliver viral vectors to spinal motor neurons utilizing retrograde axonal transport. He utilized this approach to deliver adenoviral vector carrying genes encoding nerve growth factor to the spinal cord and published his findings in 4 papers and has 3 additional manuscripts either in press or submitted for review. His work with Dr. Imperiale focused on development of adenoviral and adeno-associated viral (rAAV) vectors. He constructed a recombinant adenovirus and rAAV vectors that produces biologically active IGF-I and plans to determine if it promotes neuron survival in injured spinal cord. During this period, he applied for and was awarded 3 research grants focusing on adenoviral neurotrophic gene transfer to spinal cord and the use of adenoviral and rAAV vectors in treatment of ALS.

Dr. Boulis has recently accepted a position within the Department of Neurosurgery at the Cleveland Clinic. His clinical/research directive is to develop a laboratory for gene-based modulation of the central nervous system, a program that has been given high priority by this Department. In addition to his appointment in Cleveland, Dr. Boulis will continue to oversee and consult on experiments to evaluate the potential of viral vectors to deliver growth factors to injured spinal cord that will be conducted by the Program for Understanding Neurological Disease at the University of Michigan. He also serves as a consultant to the ALS Therapy Development Foundation in studies to develop rAAV gene therapy for the treatment of ALS. In summary, Dr. Boulis is clearly a highly motivated individual who has demonstrated an ability to not only carry out clinical work but also to develop and conduct sophisticated research. Considering the breadth of Dr. Boulis' research training, it seems unreasonable to place Dr. Boulis in the category of inexperienced clinician-scientist. The application itself, which is very well written and thought out, illustrates the level of competence that Dr. Boulis has achieved.

Career Development Plan: The primary emphasis of the proposed training plan is for Dr. Boulis to work with Dr. Amiya Banerjee, a virologist skilled in basic mechanisms of viral pathogenicity, with the goal of enhancing his understanding of virology and specifically of the use of rAAV in therapies to treat central nervous system disorders. Much of the training represents an extension of many

of the techniques that Dr. Boulis has already applied to other research problems. One of the focuses of his training will be viral tropism, with an emphasis on developing ways to promote specific tropism of rAAV in the nervous system. This is currently an important area of study within the field of gene therapy. Dr. Boulis teaching responsibilities will be limited to residents and fellow in the clinical setting, duties that the applicant indicates should not interfere with his research commitment. In addition to research, Dr. Boulis will be encouraged to attend weekly virology journal club meetings and various departmental seminars. Dr. Boulis is requesting 5 years of support for his training. In view of the advanced status of his training at this point, this time period should be more than sufficient for the applicant to reach a point to be able to successfully compete for research funding through traditional grant mechanisms (e.g. R01).

Research Plan: The goal of the research plan is to develop a viral vector capable of exhibiting both neural tropism and neuromodulation. The experiments themselves will focus on generating an rAAV vector the exhibits motor neuron tropism and is capable of inhibiting synaptic transmission. The model system that will be used is the spinal reflex arc, a simple neural circuit, which functions abnormally in animal models of spasticity. It is hoped that the results of the proposed studies will improve rAAV vector design for treatment of motor neuron disease (ALS) and for use in modulation of neural function. The proposal has 3 aims: 1) construct novel vectors capable of inhibiting synaptic transmission, 2) develop rAAV vectors that exhibit tropism for motor neurons, 3) evaluate viral vectors carrying anti-spasticity transgenes to ameliorate spasticity in the spastic mouse and in rats with spinal cord contusion injuries. The problem of viral tropism is currently a critical issue in gene therapy development for treatment of central nervous system disorders. The proposed experiments attempting to modify the rAAV capsid protein itself and/or covalent binding of neurotropic proteins to the rAAV capsid are timely, and if successful, will help to move the field of neural gene therapy forward. In Aim 3B, the applicant proposes to examine 3 different titers of virus to examine the dose response issue associated with gene therapy. The injection of virus into the sciatic nerve and the cord injury will be conducted simultaneously. The animals will be tested biweekly using behavioral measures of reflex activity and, at the end of 4 weeks, bilateral, monosynaptic reflex potentials will be measured. One of the problems associated with this design is that 4 weeks may not be sufficient time to allow the expression of the rAAV transgene to reach clinically significant levels. In summary, the specific experiments proposed under each aim are well designed and there is sufficient preliminary data presented so that it is clear that the applicant should have little trouble carrying out these experiments. The proposal itself is of R01 quality, clearly reflecting the high level of scientific competence of the applicant.

Mentor: Dr. Amiya Banerjee is a leading researcher in virology with over 627 published manuscripts. He is currently directing the research of 10 Ph.D. level scientists and indicates that he has mentored NRSA funded post-doctoral work. Dr. Banerjee carefully describes the role that he intends to play in Dr. Boulis' training. During the first 2 years, he proposes to provide extensive guidance and supervision, assisting with the design and execution of the experiments. This level of involvement will be reduced in year 3, and by year 4 Dr. Banerjee suggests that Dr. Boulis will be capable of independent work and will be in a position to begin applications for research grants. The research

training timeline outlined by Dr. Banerjee is consistent with this reviewer's suggestion that the total time needed for Dr. Boulis to attain independent research status is less than the 5 year period proposed by the applicant.

Environment and Institutional Commitment: Dr. Boulis' vector work will be conducted in Dr. Banerjee's laboratory within his P2 facility. Dr. Banerjee's laboratory occupies 1,200 sq. ft. and is situated nearby the laboratories of several other investigators who also focus on molecular virology and cellular gene expression. Dr. Banerjee's laboratory currently houses 10 Ph.D. level scientists. The applicant and his 2 technicians have access to all shared equipment facilities within the Department of Virology and a core facility that provides oligonucleotides, oligopeptides and access to confocal microscopy and a phosphoimager. The Department of Neurosurgery has set aside an area for BSL 2/2+ level research that will allow delivery of viral vectors to animals. They have also committed to provide office space to Dr. Boulis.

The Department of Neurosurgery has committed to protecting 50% of Dr. Boulis' time for research during the first 2 years of his appointment regardless of whether this award is made. The Department will continue this protection only if Dr. Boulis' is able to obtain extramural salary support. One hopes that Dr. Boulis' research career will not be entirely subject to the variations in funding that often occur as a result of changes in government research spending. One indicator of the commitment level of the Neurosurgery Department is that the Department is currently aggressively recruiting staff level neurosurgeons whose presence will help to decrease the clinical pressure on Dr. Boulis and other clinician-scientists working in the Neuromodulation Program.

ADMINISTRATIVE CRITIQUES:

HUMAN SUBJECTS/GENDER, MINORITY AND CHILDREN: Not applicable.

ANIMAL WELFARE: There is concern about the lack of detail on animal usage in this proposal. The IACUC application for the proposed experiments has not yet been approved. In general, little effort has been made by the applicant to provide a careful outline of the design of the proposed experiments in regard to animal number. The number of animals required for these studies is not explicitly stated. There is no indication how many animals will receive subcutaneous and endotracheal injections of adenovirus to test for liver or lung toxicity. The number of rats required for all sections of Aim 2A is not provided and there is no value given for Aim 2B. Group values are provided for experimental groups in Aim 3 but not the control groups. There is also some concern about the levels of discomfort that the animals may experience and what criterion the applicant will utilize to determine if treatment or euthanasia is appropriate. The effects of the viral transgenes as well as the consequences of spinal cord injury could be significant. It is assumed that the IACUC committee will address these issues and that this award will not be made until the applicant obtains proper approval from the committee.

BIOHAZARDS: No concern.

BUDGET: The applicant indicates that construction of the viral vectors described in this proposal will be funded in part by the PFUND, a fund that is also supporting rAAV viral vector development for delivery of therapeutic

growth factors.

OTHER CONSIDERATIONS: None.

FOREIGN INSTITUTION: Not applicable.

NOTICE: The NIH has modified its policy regarding the receipt of amended applications. Detailed information can be found by accessing the following URL address: <http://grants.nih.gov/grants/policy/amendedapps.htm>

NIH announced implementation of Modular Research Grants in the December 18, 1998 issue of the NIH Guide to Grants and Contracts. The main feature of this concept is that grant applications (R01, R03, R21, R15) will request direct costs in \$25,000 modules, without budget detail for individual categories.

Further information can be obtained from the Modular Grants Web site at

<http://grants.nih.gov/grants/funding/modular/modular.htm>

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ASSOCIATE PROFESSOR
UNIVERSITY OF PITTSBURGH
PATHOLOGY/BIOMED SCI TOWER RM417
PITTSBURGH, PA 15261

DI MONTE, DONATO A, MD
DIRECTOR
DEPARTMENT OF BASIC RESEARCH
THE PARKINSON'S INSTITUTE
SUNNYVALE, CA 94089-1605

ETGEN, ANNE M., PHD *
PROFESSOR
NEUROSCIENCE & PSYCHIATRY
ALBERT EINSTEIN COLLEGE OF MEDICINE
1300 MORRIS PARK AVENUE
BRONX, NY 10461

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PROFESSOR
DEPT OF NEUROSCIENCES
BROWN UNIVERSITY
PROVIDENCE, RI 02912

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PROFESSOR OF NEUROLOGY
DEPARTMENT OF NEUROLOGY
SCHOOL OF MEDICINE
UNIVERSITY OF CALIFORNIA SAN FRANCISCO
SAN FRANCISCO, CA 94143-0453

GONZALEZ, R. GILBERTO, MD, PHD
DIRECTOR OF NEURORADIOLOGY
DEPARTMENT OF RADIOLOGY
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL
BOSTON, MA 02114

GRIGGS, ROBERT C., MD
PROFESSOR AND CHAIR
DEPARTMENT OF NEUROLOGY
UNIVERSITY OF ROCHESTER
ROCHESTER, NY 14642-8673

HACKNEY, DAVID B., MD
PROFESSOR
DEPARTMENT OF RADIOLOGY
RADIOLOGY RESEARCH ADMINISTRATION
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104-2644

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NST

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HAUSER, WILLARD A, MD
PROFESSOR
DEPARTMENT OF NEUROLOGY AND PUBLIC
HEALTH
COLUMBIA COLLEGE OF PHYSICIANS AND
SURGEONS
NEW YORK, NY 10032

HECKMAN, CHARLES J., PHD *
ASSOCIATE PROFESSOR
DEPT OF PHYSIOLOGY AND PHYSICAL
MEDICAL AND REHAB
NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
CHICAGO, IL 60611

HULSEBOSCH, CLAIRE E., PHD *
PROFESSOR
DEPARTMENT OF ANATOMY & NEUROSCIENCE
MARINE BIOMEDICAL INSTITUTE
UNIVERSITY OF TEXAS MEDICAL BRANCH
GALVESTON, TX 77555-1069

LEHMAN, MICHAEL N., PHD *
PROFESSOR
DEPARTMENT OF CELL BIOLOGY,
NEUROBIOLOGY AND ANATOMY
UNIVERSITY OF CINCINNATI
COLLEGE OF MEDICINE
CINCINNATI, OH 45267

LIPKIN, IAN, MD *
PROFESSOR
DEPARTMENT OF ANATOMY & NEUROLOGY
UNIVERSITY OF CALIFORNIA, IRVINE
IRVINE, CA 92697-4292

LUNDELL, MARTHA J., PHD *
ASSISTANT PROFESSOR
UNIVERSITY OF TEXAS AT SAN ANTONIO
DEPT OF BIOLOGY
6900 NORTH LOOP 1604 WEST
SAN ANTONIO, TX 78249

LYNCH, DAVID R., MD, PHD *
ASSISTANT PROFESSOR
UNIVERSITY OF PENNSYLVANIA
CHILDRENS HOPITAL
PHILADELPHIA, PA 19104

MIZRAHI, ELI M, MD
PROFESSOR
DEPARTMENT OF NEUROLOGY
BAYLOR COLLEGE OF MEDICINE
HOUSTON, TX 77030

MORELL, PIERRE, PHD *
PROFESSOR
DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF NORTH CAROLINA
NEUROSCIENCE CENTER
CHAPEL HILL, NC 27599

NAVIA, BRADFORD A., MD, PHD
ASSOCIATE PROFESSOR
NEW ENGLAND MEDICAL CENTER
DEPARTMENT OF NEUROLOGY & PSYCHIATRY
TUFTS UNIVERSITY
BOSTON, MA 02111

NISHI, RAE, PHD
PROFESSOR
DEPT. OF ANATOMY AND NEUROBIOLOGY
UNIVERSITY OF VERMONT COLLEGE OF
MEDICINE
BURLINGTON, VT 05405

OPPENHEIM, RONALD W., PHD *
PROFESSOR
DEPARTMENT OF NEUROBIOLOGY AND ANATOMY
WAKE FOREST UNIVERSITY
BOWMAN GRAY SCHOOL OF MEDICINE
WINSTON-SALEM, NC 27157

OXFORD, GERRY S., PHD *
PROFESSOR
DEPARTMENT OF CELL AND MOLECULAR
PHYSIOLOGY
UNIVERSITY OF NORTH CAROLINA AT
CHAPEL HILL
452 MEDICAL SCIENCE RESEARCH BUILDING
UNC SCHOOL OF MEDICINE; CB #7545
CHAPEL HILL, NC 27599-7545

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PAULSEN, JANE S., PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY AND NEUROLOGY
UNIVERSITY OF IOWA
COLLEGE OF MEDICINE
IOWA CITY, IA 52242-1057

PHILLIPS, PETER C., MD *
PROFESSOR OF NEUROLOGY, ONCOLOGY AND
PEDIATRICS
DEPARTMENT OF NEUROLOGY
CHILDREN'S HOSPITAL OF PHILADELPHIA
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104-4399

ROSS, CHRISTOPHER A., MD, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY AND
NEUROSCIENCE
JOHNS HOPKINS UNIVERSITY SCHOOL OF
MEDICINE
BALTIMORE, MD 21205-2196

SEMPLE-ROWLAND, SUSAN L., PHD *
ASSOCIATE PROFESSOR
UNIVERSITY OF FLORIDA BRAIN INSTITUTE
COLLEGE OF MEDICINE
DEPT OF NEUROSCIENCE
GAINESVILLE
FL 326100244

SIMON, ROGER P., MD
DIRECTOR, NEUROBIOLOGY RESEARCH
DEPARTMENT OF MOLECULAR & CELLULAR
NEUROSCIENCE
LEGACY HEALTH SYSTEM
HOLLADAY PARK MEDICAL CENTER
1225 N.E. SECOND AVENUE, ROOM 472
PORTLAND, OR 97232

WAGNER, FRANKLIN C., PHD *
PROFESSOR
NEUROSURGERY DEPARTMENT
UNIVERSITY OF ILLINOIS
CHICAGO, IL 60612

MAIL REVIEWER
LEVINE, STEVEN R., MD
PROFESSOR OF NEUROLOGY
THE MOUNT SINAI SCHOOL OF MEDICINE
DEPARTMENT OF OF NEUROLOGY
STROKE PROGRAM
NEW YORK, NY 10029-6574

MOCZYDLOWSKI, EDWARD G., PHD
YALE UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF PHARMACOLOGY
STERLING HALL
NEW HAVEN, CT 06520-8066

SCIENTIFIC REVIEW ADMINISTRATOR
SAAVEDRA, RAUL A., PHD
SCIENTIFIC REVIEW ADMINISTRATOR
SCIENTIFIC REVIEW BRANCH
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